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The relationship between HbA1c and the functional outcome of acute ischemic stroke: A prospective cohort study

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Keywords
Hemoglobin A1C; Acute Ischemic Stroke; Outcome; Cohort Studies

Abstract

Background: High fasting blood sugar (FBS), hemoglobin A1C (HbA1c), and random glucose levels have been associated with poor neurological outcomes in patients with acute ischemic stroke (AIS). This study aimed to determine the prognostic value of HbA1c in predicting stroke's functional outcome.

Methods: In this prospective cohort study, one-hundred patients with AIS who were admitted to the Imam Khomeini Hospital Complex, Tehran, Iran, from March 2019 to February 2020, within 72 hours of symptom onset were included. A 3-month modified Rankin Scale (mRS) was used to assess the functional outcome. Patients were divided into 3 groups based on the HbA1c levels: low HbA1c level (≤ 5.6%), moderate HbA1c level (5.7%-6.4%), and high HbA1c level (≥ 6.5%). Using chi-square test, t-test, analysis of variance (ANOVA), multiple logistic regression, and receiver operating characteristic (ROC) analysis, we studied the association and prognostic value of HbA1c levels and 3-month mRS as an outcome. The significance level was considered as $P < 0.05$.

Results: We included 100 patients (53 men) with a mean age of 71.55 ± 11.94 years. The mean HbA1c, National Institutes of Health Stroke Scale (NIHSS), and mRS scores at admission were 6.98 ± 2.34, 8.27 ± 4.40, and 3.01 ± 1.47, respectively. Three-month mRS scores were significantly higher in patients with high HbA1c levels (3.43 ± 1.88) compared with low HbA1c levels (0.43 ± 0.61) and moderate HbA1c levels (1.72 ± 1.45) ($P < 0.001$).

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ROC analysis showed an area under the curve (AUC) of 0.897, and a serum HbA1c level at admission threshold of 6.15% had a sensitivity of 95.2% and a specificity of 77.6% to predict the poor outcome [95% confidence interval (CI): 0.837-0.957].

Conclusion: Our findings indicated that serum HbA1c levels at admission could be a valuable predictor of the functional outcome of patients with AIS.

Introduction

In 2019, stroke incidence exceeded 12 million, with 101 million prevalent cases, 143 million disability-adjusted life years (DALYs) lost to stroke, and 655 million deaths from stroke. Stroke remains the second greatest cause of death globally.[1] Approximately 30% of people experiencing ischemic stroke had diabetes mellitus (DM).[2] Hyperglycemia exacerbates the symptoms of a stroke by raising oxidative stress, triggering systemic inflammation, and increasing vascular permeability. Platelet accumulation and endothelial adhesion are more severe in ischemic stroke patients with diabetes or hyperglycemia.[3,4] Furthermore, as a result of acute and chronic hyperglycemia, people with DM have a poor recovery rate following stroke.[2-4] But diabetes has been considered a modifiable stroke risk factor, and it is important to manage hyperglycemia before experiencing a stroke.[5,6] There have been a few studies that show an association between hemoglobin A1C (HbA1c) levels and the functional outcome of acute ischemic stroke (AIS), and studies in Middle Eastern patients especially Iranian patients are scarce; hence, we set out this study to determine the association between HbA1c levels and the functional outcome of AIS in patients referred to an Iranian tertiary center. We also investigated the predictive ability of HbA1c in patients with functional AIS.

Materials and Methods

Study design, setting, and participants: This prospective cohort study was conducted with a census sampling method on patients with AIS admitted to Imam Khomeini Hospital Complex, Tehran, Iran, from March 2019 to February 2020, within 72 hours of symptom onset. Our study was conducted under the Declaration of Helsinki. Written informed consent was obtained before participation in the study. Participants had the right to exit the trial at any time. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran (IR.TUMS.IKHC.REC.1398.106).

Diagnostic criteria for definite AIS include: acute onset of neurologic symptoms with any severity consistent with focal brain ischemia and brain imaging suggestive of AIS.[7]

We included all patients who were admitted to our hospital with definite diagnosis of AIS.

Patients with a history of blood loss, anemia, and hemoglobinopathy, patients whose HbA1c levels were measured after 24 hours from admission, and patients who underwent intravenous (IV) thrombolysis or mechanical thrombectomy were excluded.

Study measurement: Demographic characteristics included age (year), gender (men, women), history of hypertension (HTN) (hypertensive, not hypertensive), and smoking [smoker (> 6 months), non-smoker]. The severity and classification of AIS were determined using the National Institutes of Health Stroke Scale (NIHSS) and the Trial of Org 10172 in Acute Stroke Treatment (TOAST), respectively. The modified Rankin Scale (mRS) was used to assess the functional disability of patients at admission time. The laboratory data included fasting blood sugar (FBS), HbA1c, total cholesterol, and triglyceride (TG) levels in the peripheral blood measured within 24 hours of admission. These laboratory tests were performed for all patients regardless of glucose intolerance. The outcome was 3-month mRS collected by contacting patients three months later over the phone.

The mRS is a 7-point scale from 0 to 6 that measures the functional outcomes in patients with stroke [0: the patient has no residual symptoms, 1: the patient has no significant disability, able to carry out all pre-stroke activities, 2: the patient has a slight disability, unable to carry out all pre-stroke activities but able to look after self without daily help, 3: the patient has a moderate disability, requiring some external help but able to walk without the assistance of another individual, 4: the patient has a moderately severe disability, unable to walk or attend to bodily functions without the assistance of another individual, 5: the patient has a severe disability, bedridden, incontinent, requiring continuous care, 6: the patient has expired (during the hospital stay or after discharge from the hospital)].

Mean and standard deviation (SD) were used to report quantitative variables, while number and percentage were used to report qualitative variables. All statistical analyses were conducted

using SPSS software (version 25, IBM Corporation, Armonk, NY, USA). Patients were divided into 3 groups based on the HbA1c levels: low HbA1c level (≤ 5.6%), moderate HbA1c level (5.7%-6.4%), and high HbA1c level (≥ 6.5%).

Baseline qualitative data were compared across the three groups of HbA1c with chi-square tests, and quantitative data were compared using one-way analysis of variance (ANOVA). Furthermore, to determine factors associated with the three-month follow-up outcome (poor vs. favorable outcome), an independent t-test and chi-square test were used. Moreover, to estimate adjusted factors related to the outcome, multiple linear regression was used. Receiver operating characteristic (ROC) was used to assess the diagnostic accuracy of baseline value of HbA1c in predicting the outcome of patients with ischemic stroke. An area under the curve (AUC) of more than 0.90 was considered to have high diagnostic accuracy, AUC between 0.70 and 0.90 had moderate diagnostic accuracy, and AUC of less than 0.70 had low diagnostic accuracy. The significance level was considered as $P < 0.05$.

Results

Patients' characteristics: One hundred patients (53 men) with AIS were enrolled. The mean age was 71.55 ± 11.94 years. Eighty-three individuals had HTN, and 44 were cigarette smokers. The mean NIHSS and the mean mRS scores at admission were 8.27 ± 4.40 and 3.01 ± 1.47, respectively. HbA1c levels were low in 32 individuals, moderate in 22 patients, and high in 46 patients (Table 1).

HbA1c and clinical characteristics at the time of admission: There was no significant difference between the three groups of HbA1c levels regarding gender, age, and smoking ($P = 0.115$, $P = 0.838$, $P = 0.218$, respectively) (Table 1). At the time of admission, patients with high HbA1c levels had significantly higher levels of FBS, total cholesterol, TG, NIHSS, and mRS ($P < 0.001$). On the other hand, those with low HbA1c levels had a higher HTN prevalence ($P = 0.001$).

HbA1c and 3-month functional outcome: Three-month mRS scores were significantly higher in patients with high HbA1c levels (≥ 6.5%) than in the other two groups ($P < 0.001$). Furthermore, those with a low HbA1c level (≤ 5.6%) had a lower 3-month mRS score than those with HbA1c levels between 5.7 and 6.4 ($P = 0.007$) (Table 2).

When the outcome is defined as having a good prognosis (3-month mRS: 0-1) or a poor prognosis (3-month mRS: 2-5), none of our patients died (mRS: 6) during this 3-month study. It was demonstrated that the mean HbA1c level was significantly higher in the group with a poor prognosis (8.80 ± 1.90 vs. 5.67 ± 1.66, $P = 0.001$) (Table 3). Additionally, our study showed that after controlling for confounding factors (gender, age, HTN disease, and smoking), the level of HbA1c could predict the outcome (good or poor prognosis, standardized beta coefficient = 0.747, $P < 0.001$), and the HbA1c could explain 52.6% of the total variation of the outcome (Table 4).

ROC analysis revealed an AUC of 0.897 [95% confidence interval (CI): 0.837-0.957]. A serum HbA1c cut-off of 6.15% demonstrated a sensitivity of 95.2%, specificity of 77.6%, positive predictive value (PPV) of 75.48%, and negative predictive value (NPV) of 95.71% for predicting poor outcomes (Figure 1 and Table 5).

Table 1. Patients' baseline characteristics and comparison across the three groups of hemoglobin A1c (HbA1c)

Variable	Full cohort (n = 100)	Low HbA1c (≤ 5.6%) (n = 32)	Medium HbA1c (5.7%-6.4%) (n = 22)	High HbA1c (≥ 6.5%) (n = 46)	P
Gender (men)	53 (53.0)	20 (62.5)	15 (68.2)	18 (39.1)	0.115
Age (year)	71.55 ± 11.94	70.93 ± 14.44	70.81 ± 10.73	72.32 ± 10.72	0.838
Hypertensive	83 (83.0)	31 (96.9)	13 (59.1)	39 (84.8)	0.001
Smoker	44 (44.0)	16 (50.0)	12 (54.5)	16 (34.8)	0.218
Baseline HbA1c (%)	6.98 ± 2.34	-	-	-	-
Baseline FBS (mg/dl)	142.00 ± 57.08	119.03 ± 42.06	112.77 ± 42.99	171.95 ± 58.11	< 0.001
Baseline total cholesterol (mg/dl)	165.06 ± 44.16	136.37 ± 38.74	167.95 ± 28.74	183.63 ± 43.92	< 0.001
Baseline TG (mg/dl)	138.51 ± 61.78	104.87 ± 56.68	121.13 ± 47.37	170.21 ± 56.19	< 0.001
Atrial fibrillation	3 (3.0)	-	-	-	-
Baseline NIHSS	8.27 ± 4.40	5.15 ± 4.04	8.36 ± 3.17	10.39 ± 3.90	< 0.001
Baseline mRS	3.01 ± 1.47	1.84 ± 1.19	2.86 ± 0.99	3.89 ± 1.25	< 0.001

Data are presented as number (percent) or mean ± standard deviation (SD)
HbA1c: Hemoglobin A1c; FBS: Fasting blood sugar; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale; TG: Triglyceride

Table 2. Three-month modified Rankin Scale (mRS) in different hemoglobin A1c (HbA1c) groups

P	Low HbA1c (n = 32)	Medium HbA1c (n = 22)	High HbA1c (n = 46)
	0.43 ± 0.61	1.72 ± 1.45	3.43 ± 1.88
Low vs. medium: 0.007 Low vs. high: < 0.001 Medium vs. high: < 0.001			

HbA1c: Hemoglobin A1c

Table 3. Hemoglobin A1c (HbA1c) levels and outcome

	Good outcome (n = 58)	Poor outcome (n = 42)	P
HbA1c	5.67 ± 1.66	8.80 ± 1.90	< 0.001
Low HbA1c	32 (100)	0 (0)	< 0.001
Medium HbA1c	14 (63.6)	8 (36.4)	
High HbA1c	12 (26.1)	34 (73.9)	

Data are presented as number (percent) or mean ± standard deviation (SD)
HbA1c: Hemoglobin A1c

Discussion

The current study aimed to determine the association between HbA1c levels and the functional outcome of ischemic stroke.

Hyperglycemia has been shown to be a crucial prognostic factor in stroke. Some pathophysiologic processes have been suggested for this role. Hyperglycemia impairs recanalization by increasing coagulation and decreasing fibrinolytic activity. Furthermore, hyperglycemia can decrease cerebral blood flow through inhibition of vasodilatation, generated by reduction in vasodilating agents such as nitric oxide, which is synthesized by endothelial nitric oxide synthase (eNOS) and increased formation of vasoconstrictive agents such as thromboxane A2 (TxA2) by stimulating the lipoxygenase (LOX) and cyclooxygenase (COX) pathways. Oxidative stress increased by overproduction of reactive oxygen species (ROS), such as superoxides and peroxides, in hyperglycemic states results in damage to various cell components, such as lipids, proteins, and deoxyribonucleic acid (DNA), which can lead to impairments in blood-brain barrier (BBB) function, as well as edema formation, increased infarct volume, and ultimately neuronal death. Hyperglycemia is associated with increased expression of several proinflammatory factors, such as nuclear factor κB (NF-κB) during tissue ischemia. These proinflammatory factors' overproduction and increased inflammatory response leads to promoting the adhesion of inflammatory cells and breakdown of the BBB, which enhance diapedesis of inflammatory cells out of the circulation into the interstitium of the brain and edema formation, resulting in further tissue injury and increased infarct size. In hyperglycemic conditions, anaerobic glycolysis induces accumulation of lactic acid which is proposed to associate with increased brain injury.[8] An increased frequency of hemorrhagic complications has also been linked to hyperglycemia.[3]

In accordance with previous studies, we observed a positive correlation between HbA1c levels and mRS at admission and three months later; HbA1c was able to predict the functional prognosis of the patients.[9,10]

As HbA1c is a biochemical marker reflecting the average glycaemic control over the last 3 months,[11] our results manifest the effects of long-term exposure to hyperglycemia in ischemic stroke and patients' outcomes.

Previous studies showed that a higher HbA1c level at admission was associated with an unfavorable outcome in patients with ischemic stroke.[10] Similarly, our results indicated that a higher HbA1c level, especially more than 6.4%, was significantly associated with an increased risk of severe stroke symptoms and morbidity (higher NIHSS and mRS scores) at admission.

Table 4. Regression analysis for predicting three-month modified Rankin Scale (mRS) scores

Variable	Standardized beta coefficient	P	R^2	R^2 change
Age	-0.020	0.772	0.563	0.526
Gender	-0.088	0.235		
Hypertension	-0.069	0.323		
Smoking	0.040	0.597		
HbA1C	0.747	< 0.001		

HbA1c: Hemoglobin A1c

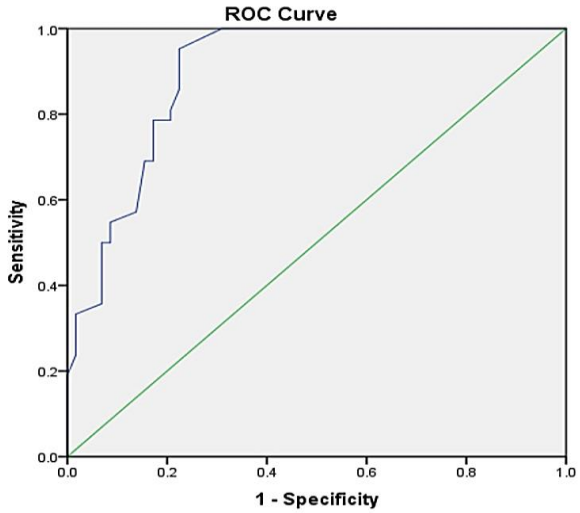

Figure 1. Receiver operating characteristic (ROC) curve of admission hemoglobin A1c (HbA1c) level for predicting poor functional outcome

Moreover, patients with high HbA1c levels had significantly higher total cholesterol and TG levels at admission time. We found higher rates of HTN in patients with higher HbA1c levels, which could be justified by the notion that HTN is the major vascular risk factor for ischemic stroke alongside diabetes.[12]

Table 5. Receiver operating characteristic (ROC) analysis of hemoglobin A1c (HbA1c) thresholds for predicting poor functional outcome in acute ischemic stroke (AIS)

Parameter	Value
AUC (95% CI)	0.89 (0.83-0.95)
Threshold HbA1c (%)	6.15
Sensitivity (%)	95.20
Specificity (%)	77.60
PPV (%)	75.48
NPV (%)	95.71

AUC: Area under the curve; CI: Confidence interval; HbA1c: Hemoglobin A1c; PPV: Positive predictive value; NPV: Negative predictive value

Our findings revealed that higher HbA1c level was associated with an increased risk of poor functional outcome in short-term follow-up (3 months), which was indicated with significantly higher levels of HbA1c in patients with poor outcome (mRS: 2-6) in comparison with patients with the mRS score of 0-1. A similar relationship between HbA1c level and functional outcome was described by Bao and Gu.[9]

ROC analysis revealed that serum HbA1c level was a predictor of the outcome with a threshold level of 6.15%, a sensitivity of 95.2%, and a specificity of 77.6%. In contrast, the study by Sung et al. showed that HbA1c was not a significant outcome predictor.[13] However, this may be related to differences in stroke severity between our research and theirs. The majority of their participants had mild to moderate stroke severity, with a median NIHSS score of 4 (2-8) upon admission, but our sample's mean NIHSS score was 8.27 ± 4.40, suggesting that the impact of hyperglycemia may be more significant in patients with severe stroke.

A limitation of this study was insufficiency of the sample size to fully exclude confounding variables. Another limitation was the categorization of patients as non-diabetic (HbA1c level: 5.6%), pre-diabetic (HbA1c level: 5.7%-6.4%), and diabetic (HbA1c level: 6.5%), without considering the severity of diabetes by further categorizing patients with DM based on their HbA1c levels.

Conclusion

Our results demonstrated that serum HbA1c levels at admission could serve as a valuable predictive factor for evaluating the functional outcome of patients with ischemic stroke with acceptable sensitivity and specificity, enabling the implementation of necessary care.

Conflict of Interests

The authors declare no conflict of interest in this study.

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